AD_____

Award Number: W81XWH-09-1-0296

TITLE: Vaccination with Dendritic Cell Myeloma Fusions in Conjunction with Stem Cell Transplantation and PD-1 Blockade

PRINCIPAL INVESTIGATOR: David Avigan, M.D.

CONTRACTING ORGANIZATION: Beth Israel Deaconess Medical Center
Boston, MA 02215

REPORT DATE: May 2012

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
May 2012	Annual	1 May 2011 – 30 April 2012

4. TITLE AND SUBTITLE

Vaccination with Dendritic Cell Myeloma Fusions in Conjunction with Stem Cell Transplantation and PD-1 Blockade

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-09-1-0296

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

David Avigan, M.D.

E-Mail: davigan@bidmc.harvard.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Beth Israel Deaconess Medical Center
Boston, MA 02215

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
Most patients with multiple myeloma achieve a complete or near complete response following autologous transplantation. However, patients experience disease relapse from a persistent reservoir of chemotherapy resistant disease. There has been strong interest in developing immunotherapeutic strategies to eradicate residual disease following autologous transplantation. Our group has developed a tumor vaccine model whereby dendritic cells are fused with tumor cells. In clinical trials, vaccination with fusion cell results in anti-tumor immune and disease responses in a subset of patients. However, vaccine efficacy is blunted by tumor mediated immune suppression and the increased presence of regulatory T cells characteristic of patients with malignancy. An important element contributing to tumor mediated immune suppression is the PD-1/PDL-1 pathway. PD-L1 exerts a significant role in promoting T cell tolerance by binding PD-1 on activated T cells and suppressing their capacity to secrete stimulatory cytokines. We have demonstrated that blockade of this pathway results in enhanced immune responses to DC/myeloma fusion cells ex vivo. In the proposed study, we will examine toxicity, immunologic effect and clinical efficacy of CT-011 therapy following stem cell transplantation for patients with myeloma. These endpoints will then be assessed in patients undergoing combined therapy with the vaccine and antibody.

15. SUBJECT TERMS
DC/myeloma fusion vaccine, PD1 blockade, immunotherapy, multiple myeloma

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	11	19b. TELEPHONE NUMBER *(include area code)*

Table of Contents

A. INTRODUCTION

In this project, we are conducting a clinical trial in which patients with multiple myeloma are treated with an anti-PD1 antibody (CT-011) alone (Cohort 1) and in conjunction with a dendritic cell/myeloma fusion cell vaccine (Cohort 2) following autologous transplantation. The goal of the project is determine the effect of CT-011 alone, and in conjunction with a DC/myeloma fusion cell vaccine, to stimulate effective anti-tumor immunity and disease response.

B. BODY

Clinical Trial

The clinical study is being conducted in two stages. In the first stage, a pilot study is being conducted in which patients are treated with CT-011 alone following autologous transplant. The primary objective of this stage is to explore immunologic responses to CT-011 in the post-transplant period. The secondary objective is to assess the toxicity of treating patients with CT-011 in the post-transplant setting.

In the second stage, patients will receive a combination of CT-011 and DC/myeloma fusion vaccination. The primary objective is to determine if cellular immunity is induced by treatment with monoclonal antibody CT-011 and DC/myeloma fusion cells in conjunction with stem cell transplant. The secondary objectives of this stage are: 1) To assess the toxicity associated with treating multiple myeloma patients with monoclonal antibody CT-O11 in combination with DC/myeloma fusion vaccine following autologous transplant, 2) To correlate levels of circulating activated and regulatory T cells with immunologic response, and 3) To define anti-tumor effects using serum markers, radiological studies, and time to disease progression.

The targeted study population includes patients with multiple myeloma who are potential candidates for high dose chemotherapy with stem cell rescue. On April 25, 2011, the study received IRB approval to increase study enrollment to cohort 1 to a maximum of 20 evaluable participants; evaluable is defined by having received two or more treatments. When 10

participants in cohort 1 have received two infusions of CT-011, enrollment to cohort 2 will begin. Cohort 2 will enroll 25 evaluable participants. In cohort 1, participants will receive three infusions of CT-011 at doses of doses of 3mg/kg given at 6 week intervals beginning 1-3 months following autologous transplant. In cohort 2, participants will receive three infusions of CT-011 given at six week intervals, in conjunction with vaccination with DC/myeloma fusion cells. Vaccination will be given one week before each infusion of CT-011 and will be given in conjunction with GM-CSF on the day of vaccination and for three days thereafter.

Status: The protocol (DF-HCC protocol number 09-061) is open to accrual at the DF/HCC as of March 19, 2010. Rambam Medical Center (RMC) in Haifa, Israel was added on April 26, 2011. As of May 1, 2012, 32 patients have been screened. There have been seven screen failures: four patients did not meet eligibility criteria and three patients elected to pursue only standard of care therapy. To date, 25 participants have met eligibility criteria and have been enrolled: 19 participants at DF/HCC and six participants at RMC.

Eight participants have come off study. One participant at DF/HCC came off study at five months following completion of study treatment for disease progression. Seven participants came off study prior to initiating study treatment: six at DF/HCC and one at RMC. At DF/HCC, three participants came off study to pursue only standard of care therapy, one participant for disease progression during induction chemotherapy. In addition, two participants died during standard of care induction chemotherapy, before initiating study treatment. One participant died on 11/5/10 after suffering a cardiac arrest in his home; the event was reported to the Dana Farber Harvard Cancer Center IRB on 11/11/10. Another participant committed suicide on 1/19/12; the event was reported to the Dana Farber Harvard Cancer Center IRB on 1/20/12. Although the unrelated deaths did not meet reporting criteria to the FDA, both were nevertheless communicated to the FDA as the events were representative of deaths on study (FDA1571: S268 sent on 11/15/10, and FDA1571: S295 sent on 1/20/12,). At RMC, one participant came off study prior to initiating study treatment to pursue only standard of care therapy.

Currently, 17 participants are enrolled to the study: 12 at DF/HCC and five at RMC. Of the subjects who are enrolled at DF/HCC, two have completed study treatment, active follow-up and

are now in long-term follow-up; one has completed treatment and is now in active follow-up; two are currently receiving treatment; four have undergone autologous stem cell transplant and are awaiting the initiation of treatment; three have undergone tumor collection for DTH skin testing and are completing pre-transplant chemotherapy. Of the five subjects who are enrolled at RMC, one has completed treatment and is now in active follow-up, one is currently receiving study treatment; two have undergone autologous stem cell transplants and are awaiting the initiation of treatment; one has undergone tumor collection for DTH skin testing and is completing induction chemotherapy.

Subject Study Information

Screen Failures

Subject Initials	Screening Number	Consent Date	Age	Gender	Race/ Ethnicity	Reason
ES	2	5/25/10	54	F	White	Failure to meet eligibility criteria
JP	5	7/16/10	51	M	Hispanic	Failure to meet eligibility criteria
GW	7	10/28/10	59	M	White	Failure to meet eligibility criteria
JD	13	5/3/2011	51	M	White	Failure to meet eligibility criteria
EB	18	7/25/11	62	F	African American	Elected to pursue standard of care therapy only
JH	19	8/15/11	72	F	White	Elected to pursue standard of care therapy only
JR	30	12/6/11	61	M	Hispanic	Failure to meet eligibility criteria

Subjects Enrolled

Subject Initials	Site	Screening Number	Enrollment Number	Consent Date	Registration Date	Age	Gender	Race/ Ethnicity	Off -Study Date	Reason Off-Study
LC	DF/HCC	1	1	5/10/2010	5/13/2010	48	M	White	8/14/2010	Disease Progression
RG	DF/HCC	3	2	6/23/2010	7/2/2010	70	M	White	11/5/2010	Death
RP	DF/HCC	4	3	7/1/2010	7/9/2010	52	F	Black	N/A	N/A
CC	DF/HCC	6	4	9/16/2010	9/29/2010	55	M	White	12/12/2011	Disease Progression
KF	DF/HCC	8	5	12/21/2010	12/30/2010	55	F	White	N/A	N/A

Subject Initials	Site	Screening Number	Enrollment Number	Consent Date	Registration Date	Age	Gender	Race/ Ethnicity	Off -Study Date	Reason Off-Study
DW	DF/HCC	9	6	12/27/2010	1/7/2011	47	M	White	10/12/2011	Elected to pursue SOC therapy
DF	DF/HCC	10	7	12/29/2010	1/13/2011	63	M	White	N/A	N/A
GF	DF/HCC	11	8	1/3/2011	1/28/2011	73	F	White	10/19/2011	Elected to pursue SOC therapy
SM	DF/HCC	12	9	2/4/2011	2/15/2011	58	M	White	N/A	N/A
RR	DF/HCC	14	10	5/16/2011	5/18/2011	67	M	White	N/A	N/A
AG	DF/HCC	15	11	5/26/2011	6/6/2011	45	F	White	N/A	N/A
KI	RMC	16	12	6/9/2011	6/14/2011	61	M	White	11/6/2011	Elected to pursue SOC therapy
BF	RMC	17	13	7/19/2011	7/21/2011	64	F	White	N/A	N/A
RB	DF/HCC	20	14	8/22/2011	8/26/2011	58	M	White	3/1/2012	Elected to pursue SOC therapy
SMM	RMC	21	15	9/5/2011	9/12/2011	55	M	White	N/A	N/A
FM	DF/HCC	22	16	10/12/2011	10/26/2011	50	M	Hispanic	N/A	N/A
ES	DF/HCC	23	17	11/3/2011	11/10/2011	55	F	White	N/A	N/A
KM (Male)	DF/HCC	24	18	10/21/2011	11/10/2011	49	M	Black	1/19/2012	Death
KM (Female)	DF/HCC	25	19	11/17/2011	11/21/2011	56	F	White	N/A	N/A
KR	RMC	26	20	11/22/2011	11/30/2011	47	M	White	N/A	N/A
NP	DF/HCC	27	21	12/16/2011	12/21/2011	62	F	White	N/A	N/A
RT	RMC	28	22	1/5/2012	1/9/2012	66	F	White	N/A	N/A
BB	DF/HCC	29	23	1/20/2012	1/30/2012	60	M	White	N/A	N/A
TB	RMC	32	24	2/2/2012	2/3/2012	60	M	White	N/A	N/A
IC	DF/HCC	31	25	1/5/12	2/17/12	66	F	Hispanic	N/A	N/A

PARTICIPANTS RECEIVING TREATMENT

SUBJECT ID	Cohort and Dose Administered	Treatment Dates	Clinical Outcome
RP/PM3 (DF/HCC)	Cohort 1: CT-011 Alone 3 doses at 3mg/kg	#1. 2/14/11 #2. 3/28/11 #3. 5/9/11	Best response at the end of transplant was complete response. Since completing treatment, the participant has remained in a complete response.
CC/PM4 (DF/HCC)	Cohort 1: CT-011 Alone 3 doses at 3mg/kg	#1. 5/4/11 #2. 6/15/11 #3. 7/27/11	Best response at the end of transplant was complete response. The participant developed disease progression at five months following last treatment.
KF/PM5 (DF/HCC)	Cohort 1: CT-011 Alone 3 doses at 3mg/kg	#1 6/28/11 #2. 8/9/11 #3. 9/20/11	Best response at the end of transplant was complete response. Since completing treatment, the participant has remained in a complete response.
DF/PM7 (DF/HCC)	Cohort 1: CT-011 Alone 3 doses at 3mg/kg	#1. 3/6/12 #2. 4/26/12 #3. TBD	Best response at the end of transplant was very good partial response. The participant will have his disease reassessed at one month following completion of treatment.
SM/PM9 (DF/HCC)	Cohort 1: CT-011 Alone 3 doses at 3mg/kg	#1. 9/19/11 #2. 10/31/11 #3. 12/12/11	Best response at the end of transplant was very good partial response. Since completing treatment, the participant has remained stable at his best response.
RR/PM10 (DF/HCC)	Cohort 1: CT-011 Alone 3 doses at 3mg/kg	#1. 1/31/12 #2. 3/13/12 #3. 4/24/12	Best response at the end of transplant was complete response. The participant will have his disease reassessed at one month following completion of treatment.
BF/PM13 (RMC)	Cohort 1: CT-011 Alone 3 doses at 3mg/kg	#1. 1/19/11 #2. 3/1/12 #3. 4/11/12	Best response at the end of transplant was complete response. The participant will have his disease reassessed at one month following completion of treatment.
SMM/PM15 (RMC)	Cohort 1: CT-011 Alone 3 doses at 3mg/kg	#1. 4/5/12 #2. TBD #3. TBD	Best response at the end of transplant was very good partial response. The participant will have his disease reassessed at one month following completion of treatment.

In total, eight participants have initiated treatment, and seven have received at least two infusions of the study drug, and therefore, are evaluable for response. Of these seven participants, six remain without disease progression: two participants have achieved a CR, three participants have achieved a VGPR and one participant has achieved a PR. In addition, one participant, who received three infusions of the study treatment, developed progressive disease at five months following completion of treatment (10.5 months following transplant), and was subsequently removed from study. The median time without disease progression for the seven evaluable participants is 7.8 months from transplant.

Immunological Responses to Date: Immunologic response was determined by quantifying circulating tumor reactive T cells at each time point as defined by the percent T cells expressing IFNg in response to ex vivo exposure to autologous tumor lysate. Results are presented as the percentage of CD4 or CD8 T cells expressing IFNg.

Pt #	IFNg (REN)	Pre-Mobilization	Pre-Infusion #1	Pre-Infusion #2	Pre-Infusion #3	Post I month	Post 3 mpnth	Post 6 month
PM03	CD4/IFNg	0.21	0.39	1.23	3.27	1	1.85	3.42
	CD8/IFNg	0.42	3.43	11.33	13.3	3.34	4.61	9.22
PM05	CD4/IFNg	0.07	0.33	0.39	4.08	3.82	0.19	0.31
	CD8/IFNg	0.49	0.39	1.25	11.99	11.76	1.4	0.86

TREATMENT RELATED ADVERSE EVENTS

Subject ID	AE	Start Date	CTC Grade	Relationship	Action Taken Regarding TX	Outcome
PM03	Leukopenia	3/14/11	1	POSSIBLE	NONE	RESOLVED
PM03	Leukopenia	5/2/11	1	POSSIBLE	NONE	RESOLVED
PM03	Leukopenia	5/23/11	1	POSSIBLE	NONE	RESOLVED
PM03	Leukopenia	7/11/11	2	POSSIBLE	NONE	RESOLVED
PM03	Leukopenia	7/13/11	1	POSSIBLE	NONE	ONGOING
PM03	ANC	5/9/11	1	POSSIBLE	NONE	RESOLVED
PM03	ANC	5/23/11	1	POSSIBLE	NONE	RESOLVED
PM03	ANC	6/10/11	2	POSSIBLE	NONE	RESOLVED
PM03	ANC	7/11/11	3*	POSSIBLE	NONE	RESOLVED
PM03	ANC	7/13/11	1	POSSIBLE	NONE	RESOLVED
PM03	ANC	9/2/11	2	POSSIBLE	NONE	RESOLVED
PM03	ANC	9/30/11	1	POSSIBLE	NONE	ONGOING
PM03	Allergic Rhinitis	7/11/11	1	POSSIBLE	NONE	ONGOING
PM04	Diarrhea	5/5/11	1	PROBABLE	NONE	RESOLVED
PM04	Diarrhea	7/27/11	1	POSSIBLE	NONE	RESOLVED
PM04	Diarrhea	9/5/11	1	POSSIBLE	NONE	RESOLVED
PM04	Pain, Joint	8/27/11	2	POSSIBLE	NONE	RESOLVED
PM04	Night Sweats	9/3/11	1	POSSIBLE	NONE	RESOLVED
PM04	Fatigue	8/27/11	2	POSSIBLE	NONE	RESOLVED
PM04	Fatigue	9/18/11	1	POSSIBLE	NONE	RESOLVED
PM05	Diarrhea	7/7/11	1	POSSIBLE	NONE	RESOLVED
PM05	Diarrhea	7/31/11	1	POSSIBLE	NONE	RESOLVED
PM05	Diarrhea	9/27/11	1	POSSIBLE	NONE	RESOLVED
PM05	Diarrhea	10/19/11	1	POSSIBLE	NONE	RESOLVED
PM07	diarrhea	3/6/12	1	POSSIBLE	NONE	RESOLVED
PM09	Diarrhea	10/10/11	1	POSSIBLE	NONE	RESOLVED
PM09	Rash	10/1/11	2	POSSIBLE	NONE	ONGOING
PM09	Thyroid Function, Low	10/31/11	1	POSSIBLE	NONE	RESOLVED
PM09	Eosinophils, Elevated	12/12/11	1	POSSIBLE	NONE	RESOLVED
PM10	Diarrhea	2/2/12	1	PROBABLY	NONE	RESOLVED
PM10	Diarrhea	2/13/12	1	POSSIBLE	NONE	RESOLVED
PM10	Diarrhea	2/23/12	1	PROBABLY	NONE	RESOLVED
PM10	Diarrhea	4/27/12	1	PROBABLY	NONE	RESOLVED
PM10	Nausea	2/1/12	1	PROBABLY	NONE	RESOLVED
PM10	Thyroid Function, Low	3/13/12	1	POSSIBLE	NONE	RESOLVED

Subject ID	AE	Start Date	CTC Grade	Relationship	Action Taken Regarding TX	Outcome
PM15	Weakness	4/5/12	1	POSSIBLE	NONE	RESOLVED
PM15	Periorbital Swelling	4/5/12	1	POSSIBLE	NONE	RESOLVED

*The episode of grade 3 low ANC resolved to grade 1 after two days without growth factor support. This event did not meet TLT criteria.

Treatment Related Serious Adverse Events:

There have been no serious adverse events related to study treatment.

Treatment Summary of Subjects that Died While on Study:

There have been two unrelated deaths on study. The participants had not initiated study treatment. One participant died on 11/5/10 after suffering a cardiac arrest in his home; the event was reported to the Dana Farber Harvard Cancer Center IRB on 11/11/10. Another participant committed suicide on 1/19/12; the event was reported to the Dana Farber Harvard Cancer Center IRB on 1/20/12. Although the unrelated deaths did not meet reporting criteria to the FDA, both were nevertheless communicated to the FDA as the events were representative of deaths on study (FDA1571: S268 sent on 11/15/10, and FDA1571: S295 sent on 1/20/12,). At RMC, one participant came off study prior to initiating study treatment to pursue only standard of care therapy.

C. REPORTABLE OUTCOMES

There are no updated reportable outcomes since last year.

D. CONCLUSIONS

The clinical trial (DF-HCC protocol 09-061) is open to accrual at both the Dana Farber Harvard Cancer Center (Boston), and Rambam Medical Center (Haifa, Israel). To date, 25 participants have met eligibility criteria and have been enrolled: 19 participants at DF/HCC and six participants at RMC. Seven participants came off study prior to initiating study treatment. In total, eight participants have initiated treatment, and seven have received at least two infusions of the study drug, and therefore, are evaluable for response. Of these seven evaluable participants, six remain without disease progression: two participants have achieved a CR, three participants have achieved a VGPR and one participant has achieved a PR. In addition, one participant, who received three infusions of the study treatment, developed progressive disease at five months following completion of treatment (10.5 months following transplant), and was subsequently removed from study. The median time without disease progression for the seven evaluable participants is 7.8 months from transplant.

Additionally, ten participants are on study, but have not yet initiated study therapy. Six participants have undergone autologous stem cell transplant and are awaiting the initiation of treatment; four have undergone tumor collection for DTH skin testing and are completing pre-transplant chemotherapy. Once 10 participants have received at least two treatments, enrollment to cohort 2 will begin.